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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/502,235	07/22/2004	Malgorzata Anna Kisielow	1-32330A/FMI	9191

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EXAMINER	
SAJJADI, FEREYDOUN GHOTB	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 10/10/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/502,235	KISIELOW ET AL.	
	Examiner	Art Unit	
	Fereydoun G. Sajjadi	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 July 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) *13 and 21-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12, 14-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants response of July 12, 2006, to the non-final action dated January 12, 2006 has been entered. No claims were cancelled and no new claims added. Claims 1, 5, 7-11, and 16-20 have been amended. Claims 13 and 21-23 remain withdrawn from consideration, without traverse. This application contains claims drawn to an invention nonelected without traverse in the paper filed on October 21, 2005. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claims 1-23 are pending in the application. Claims 1-12, and 14-20 are under current examination.

Response to Claim Objections

Claims 1 and 11 were previously objected to in the previous office action dated January 12, 2006 for containing a preamble inconsistent with the body of the claim. In view of Applicants amendment of the claims, the previous objections are withdrawn.

Response to Claim Rejections - 35 USC § 112-Indefinite

Claims 1 and 20 were rejected under 35 USC § 112 second paragraph, in the previous office action dated January 12, 2006 as being indefinite. In view of Applicants amendment of the claims, the previous rejections are withdrawn.

Claim 16 stands rejected under 35 USC § 112 second paragraph, as being indefinite. The rejection set forth on p. 3 of the previous office action dated January 12, 2006 is maintained for claim 16, because the claim is still unclear. The claim recites the method of claim 1, wherein said specific isoform is transcribed under the control of an endogenous promoter using a knock-in construct. It is not clear whether said endogenous promoter is present in the knock-in construct (i.e. being the same promoter in an expression vector as recited in claim 1), or whether said specific isoform is introduced in the proximity of an endogenous promoter that is present in the genome of the cell.

Response to Claim Rejections - 35 USC § 112, Written Description

Claims 1-12 and 14-20 stand rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The rejection set forth on pp. 3-6 of the previous office action dated January 12, 2006 is maintained for claims 1-12 and 14-20, for reasons of record.

Applicants traverse the rejection, stating that the initial burden of establishing why a person skilled in the art would not recognize written description support for the claims, has not been met. Applicants maintain that the present Application provides adequate written description support for the elements and steps of the present method claims, and that the present claims only require a limited degree of knowledge on the part of the average practitioner, and not knowledge of every possible isoform of every gene product. Applicants note that the claims of the present invention are method claims, and as such, written description support must be provided with regards to the steps and elements of the claimed methods. Further stating that the examiner is in error in requesting proof of the adequacy of written description support for an entire genus of genes or gene families, as these are not composition of matter claims. Applicants additionally cite Example 18 from USPTO's Written Description Guidelines concluding that a particular gene product is not essential to the present method claims, and that support for the steps and elements is provided for in at least p. 10, line 27 of the present specification. Applicants arguments have been fully considered, but not found persuasive.

As was outlined in the office action of January 12, 2006, the instant claims broadly encompass a method of expressing a specific isoform of any gene product, in any cell (claim 20), or any mammalian cell (claim 1), absent other isoforms of said gene product, comprising introducing into said cell a ds RNA having at least 95% sequence identity to a common nucleic acid sequence shared by two or more isoforms of said gene product. As such, the claims require knowledge of numerous desired isoforms of a gene product, whether endogenous to said cell or isoforms that may be exogenous in origin. Knowledge of numerous isoforms would also be required to determine the nature of the sequences that would constitute a common and shared nucleic acid. The specification defines isoform "to encompass gene products that are produced as a result of differential gene splicing as well as from the use of alternative transcription start

sites. In addition, ...the term isoforms include any closely related sequences and therefore may include a mutated gene in a cell" (p. 10, lines 30-31, bridging p. 11, lines 1-4). The specification discloses only the Shc gene family as exemplary for isoforms of a signaling adaptor/scaffold gene product (Example 1, p. 17) with ShcA, as exemplary for the desired isoform (line 6, p.18) and specifically describe the use of 21-mer oligonucleotide pairs as siRNAs of Shc (lines 28-29, p. 18). However, the specification provides no description of the substantial number of genes that can express more than one isoform, or have closely related sequences thereto, in any cell, as claimed. The specification is further devoid of any description for a desired isoform replacing a mutant isoform or a tumor suppressive mutant isoform in a cell.

In response to Applicants argument that the present claims only require a limited degree of knowledge on the part of the average practitioner, and not knowledge of every possible isoform of every gene product, it should be noted that the method of the instant invention requires and is dependent on RNA interference by double stranded ribonucleic acid, that must be designed in a sequence specific manner, to form a specific secondary structure, and empirically tested to determine whether any particular double stranded sequence having 95% sequence identity to a sequence commonly shared by the different isoforms would result in proper suppression of expression of all said isoforms. The instant claims are directed to expressing a specific isoform of any gene product, whereas the limited information provided by the specification is for the Shc family and the design of an siRNA, only applicable to the Shc genes.

In response to Applicants argument that the instant claims are method claims, it is noted that claim 20 is directed to a kit, and not a method. Further, method claims encompassing a claimed genus of nucleic acid isoforms, still require an adequate written description of said genus. With regards to Example 18 of the Written Description Guidelines, involving gene expression in *Neurospora crassa*, it was concluded that "there is no substantial variation within the genus". Such is not the case where the expression of numerous isoforms of a multitude of genes may need to be suppressed by at least one siRNA molecule. The variation within the instantly claimed genus may be correctly characterized as substantial.

Applicants further argue that the practitioner of the present method only requires knowledge related to her gene product of interest, and not every possible isoform of every gene product that is capable of expression via multiple isoforms, because knowledge of other genes

would be superfluous. Applicants further argue that where characterized, such isoforms would be found using various literature and bioinformatics search tools, or determined by practicing potentially time-consuming, but routine molecular biology and biotechnology techniques. Applicants arguments have been fully considered, but not found persuasive. In response, it is noted that while a particular practitioner would require knowledge related to her gene product of interest, such knowledge is in fact absent from the instant specification, unless said practitioner wished to specifically express an isoform of the Shc gene. The lack of such guidance has been outlined above and in the previous office action. Further, Applicants arguments regarding additional experimentation are pertinent to issues of enablement, and not written description.

Therefore, the rejection of claims 1-12 and 14-20, is maintained for reasons of record and the foregoing discussion.

Reply to Claim Rejections - 35 USC § 112-Scope of Enablement

Claims 1-12 and 14-20 stand rejected under 35 U.S.C.§112, first paragraph, because the specification does not reasonably provide an enablement for the full scope of the invention. The rejection set forth on pp. 6-12 of the previous office action dated January 12, 2006 is maintained for claims 1-12 and 14-20, for reasons of record.

Applicants traverse the rejection, stating that the examiner is in error in his assertion that the method claims of the present invention require knowledge of every possible isoform of every gene product that is capable of expression via multiple isoforms, citing the arguments set forth for the written description rejections. Specifically arguing that Applicants only need to demonstrate evidence of enablement for the steps and elements of the present method claims, and not the complete set of every possible isoform of every gene product that is capable of expression via multiple isoforms. Applicants additionally respond to the unpredictability of RNAi in the prior art of Caplen et al. (Gene 2000), cited in the previous office action, by providing four references wherein the RNA interference resulted in the inhibition of gene expression. Applicants arguments have been fully considered, but not found persuasive.

The response to Applicants arguments regarding the requirement to characterize the isoforms to a gene product of interest, and to further test various siRNA sequences for their ability to specifically inhibit all isoforms of the gene, has been addressed *supra*.

As was outlined in the office action of January 12, 2006, the instant claims broadly encompass methods of expressing a desired isoform of a gene product both *in vitro* and *in vivo*, by procedures that involve delivery of nucleic acids to cells other than direct contact (aerosol delivery for instance) and for applications that may include gene therapy (claim 14 for example). The specification teaches that the mammalian cell can be any cell of interest (line 17, p. 11); and that the desired isoform may be transcribed as a transgene *in vivo*, either as si/dsRNA or in the form of a hairpin structure. The specification additionally envisions the use of the isoform for correction of aberrant isoforms, in a method for treating disease in a subject by various pharmaceutical compositions (pp. 15-17).

Claims 1, 14 and 20 of the instant application are drawn to a method of expressing a desired isoform of a broad genus of all genes encoding isoforms or whose products are modified to constitute isoforms, comprising various methods of nucleic acid delivery and under numerous conditions, including *in vivo*, for applications that may include gene therapy, not apparent from the disclosure of the invention. The instant specification provides for the inhibition of the expression of Shc gene family isoform products in HeLa tissue culture cells, *in vitro* (Example 1, p. 17) as exemplary for a gene family expressing desired and undesired isoforms of a gene. Because exposing a cell to a nucleic acid would entail numerous methods of nucleic acid

delivery, including viral, particle mediated or by aerosol administration, and further, to any mammalian cell type *in vitro* or *in vivo*, it would require undue experimentation by the skilled Artisan to carry out tests on all mammalian cell types, including living cells, and to further test the various modes of gene delivery, as claimed in claims 1, 14 and 20. The unpredictability of attenuating expression of a target gene in all types of cells, including mammalian cells, by RNA interference (RNAi) is evident in prior and post-filing art. Applicant has not addressed the foregoing issues raised in the previous office action.

Applicants have addressed the reference of Caplen et al. (Gene, 252:95-105, 2000), by providing four references wherein the RNA interference resulted in the inhibition of gene expression. The references provided by Applicant do not serve to refute the unpredictability inherent in the art of RNA interference. The instantly claimed method requires the complete suppression of expression of all isoforms, variants, mutants and closely related sequences of a gene product. As was outlined in the previous office action, the post filing art of Caplen (Expert Opin. Biol. Ther. v. 3(4):575-586, 2003) states: "Many of the problems associated with developing RNAi as an effective therapeutic are the same as encountered with previous gene therapy approaches. The key issues of delivering nucleic acids to the required tissue and cell type, while ensuring an appropriate level of efficacy with minimum toxicity induced by the vector system...". (page 581) Those of skill in the art of RNA interference are optimistic about the potential of RNA interference as a therapeutic tool, but even with the advances made subsequent to the filing of the instant application, the field recognizes that therapeutic methods are not yet effective. Thus, the post-filing art clearly suggests that administering dsRNA, either *in vitro* or *in vivo*, to attenuate expression of target genes is not a reproducible or predictable art.

Moreover, to practice the claimed invention *in vivo* a number of variables would have to be optimized, including 1). the mode of delivery of the oligonucleotide to an organism that would allow it to reach the targeted cell, 2). the amount of oligonucleotide that would need to be delivered in order to allow inhibition of the expression of a target gene once it reached the proper cell and 3). ensuring the oligonucleotide remains viable in a cell for a period of time that allows inhibition of the gene to an extent that there is a measurable and significant therapeutic effect. Each one of these variables would have to be empirically determined for each dsRNA or hairpin nucleic acid.

It is further noted that, the specification in the instant application does not teach how an expression vector encoding a desired isoform of a gene can be used effectively in administering transgene either via numerous possible routes of delivery or to a multitude of mammalian cells *in vivo* or *ex vivo*. The specification also does not provide any guidance as to how studies in HeLa tissue culture cells can be extrapolated to other cell types or human situations. Applicant's specification provides no examples of gene delivery other than plasmid mediated by transfection and no examples of RNA interference other than transfection in tissue culture. In addition, prior art at the time of filing of this application as described *supra*, does not provide any convincing guidance in this regard either. The cited art clearly indicates an unpredictable status for the practice of gene therapy pertaining to the regulation of gene expression.

Therefore, the rejection of claims 1-12 and 14-20, is maintained for reasons of record and the foregoing discussion.

Response to Claim Rejections - 35 USC § 102

Claims 1-12 and 14-20 stand rejected under 35 USC § 102(e), as anticipated by Tuschl et al. (U. S. Patent Application No.: 2004/0259247, filed Nov. 29, 2001). The rejection set forth on pp. 12-16 of the previous office action dated January 12, 2006 is maintained for claims 1-12 and 14-20, for reasons of record.

Applicants disagree with the rejection, stating that not every element of claims 1-12 and 14-20 is met by the Tuschl et al. reference. Specifically, arguing that the RNAi methods disclosed in the Tuschl et al. reference are used for knocking out a target gene of interest, and in some cases, providing a replacement copy; and that the "knockout and rescue" methodology are akin to "gene targeting" methods seen in the transgenic animal field. Whereas the present invention provides methods of isolating isoforms of interest of gene products of interest. Further stating: "The present methods allow for the study of proteins of related sequence but with biochemically and/or biologically distinct features, something not possible employing the Tuschl methodology. The present methods are unique and do not have an analogy in the transgenic animal field." Applicants arguments have been fully considered, but not found persuasive.

In response, it is noted that the invention of Tuschl et al. utilizes double stranded RNA (siRNA) for RNA interference for sequence-specific post transcriptional gene silencing

(Abstract), and is distinct from gene targeting in the transgenic field, involving the targeted alteration of genomic DNA. While Tuschl et al. use the term knockout to describe the suppression of RNA expression, Applicants are incorrect in applying the gene targeting analogy. Applicants are further incorrect in stating that the present invention "provides methods of isolating isoforms of interest of gene products of interest". The instant claims do not recite the isolation of any isoforms of a gene product. Moreover, the Tuschl et al. teach that their method may be used in analytic procedures, e.g. in the functional and /or phenotypical analysis of gene expression profiles and/or proteomes (paragraph [0036, column 2, p. 3). "Using RNAi based knockout technologies, the expression of an endogenous target gene may be inhibited in a target cell" (paragraph [0037], column 2, p. 3), further, "capable of inhibiting the expression of at least one endogenous target gene. "The endogenous gene may be complemented by an exogenous target nucleic acid coding for the target protein or a variant or mutated form of the target protein, e.g. a gene or a cDNA" (paragraph [0038], column 2, p. 3).

Applicants should be note that exogenous and endogenous target genes described by Tuschl et al. are equivalent to specific and other isoforms of a gene product respectively, as the exogenous target nucleic acid is encoding the endogenous target protein, and hence is capable of complementation. As stated by Tuschl et al. the complementation may be achieved by an exogenous target nucleic acid coding for the endogenous gene; i.e. the endogenous and exogenous target nucleic acids have identical sequences.

Applicants further argue that the Tuschl reference describes using RNAi to inhibit the expression of endogenous target genes, thereby knocking them out (i.e., suppressing their function); on the other hand, the present invention contemplates inhibiting isoforms of a gene of interest, while protecting isoforms of interest of the gene of interest. Critically, the latter allows for the investigation of the function of individual gene isoforms, while the former does not.

Such is not found persuasive. Step (a) of claim 1 involves the siRNA mediated knockout or suppression of isoform expression, followed by step (b), introduction of an expression vector encoding a specific isoform. Tuschl et al. teach RNAi or siRNA mediated knockout or suppression of an endogenous target gene in a cell, that may then be complemented by an exogenous target nucleic acid coding for the target protein or variant form of the target protein (i.e. step (b) of instant claims 1, introducing an expression vector encoding a specific isoform). It

is therefore unclear why the method of Tuschl et al. would not allow the investigation of the function of individual gene isoforms, given that the instant specification defines an isoform of a gene as any closely related sequences of said gene.

Therefore, the rejection of claims 1-12 and 14-20, is maintained for reasons of record and the foregoing discussion.

Conclusion

Claims 1-12 and 14-20, are not allowable.

THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR§1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications regarding the formalities should be directed to Patent Analyst William Phillips, whose telephone number is **(571) 272-0548**.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Fereydoun G. Sajjadi whose telephone number is **(703) 272-3311**. The examiner can normally be reached Monday through Friday, between 7:00-4:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave T. Nguyen can be reached on **(571) 272-0731**. The fax phone number for the organization where this application or proceeding is assigned is **(571) 273-8300**. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at **866-217-9197** (toll-free).

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Fereydoun G. Sajjadi, Ph.D.
Examiner, USPTO, AU 1633

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER